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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/674,581	09/29/2003	Yuuki Tsutsui	019941-001810US	5398

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EXAMINER	
HISSONG, BRUCE D	
ART UNIT	**PAPER NUMBER**
1646	

MAIL DATE	DELIVERY MODE
10/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/674,581	TSUTSUI ET AL.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7,9,13,15,19,21-27 and 31-39* is/are pending in the application.

4a) Of the above claim(s) *21-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7, 9, 13, 15, 19, 31-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/29/2007 has been entered.

2. Claims 1-4, 8, 10, 14, 16, and 28-30 were cancelled, and new claims 31-39 added, in the amendment received on 8/29/2007. Therefore, claims 7, 9, 13, 15, 19, 21-27, and 31-39 are currently pending. Claims 21-27 are withdrawn as non-elected subject matter, and claims 7, 9, 13, 15, 19, and 31-39 are the subject of this office action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 7, 9, 13, 15, and 19 *remain rejected*, and new claims 31-39 are also rejected, under 35 USC § 103(a) as being obvious in view of the combination of Staats *et al* ("Staats", WO00/20028) and Takasu (*Kurume Med. J.*, 2001, Vol 48, p. 171-174) as set forth on pages 2-4 of the office action mailed on mailed on 5/29/2007 and pages 5-7 of the office action mailed on 12/14/2006.

The claims of the instant invention are drawn to a mucosal vaccine adjuvant comprised of a vaccine antigen and a natural IFN-α, wherein the vaccine antigen is a protein or peptide antigen, wherein nasal mucosal administration of said mucosal adjuvant/vaccine antigen induces both vaccine antigen-specific antibody in blood and vaccine antigen-specific antibody secreted at the mucosal surface. The claims are also drawn to a combined product of a vaccine antigen and mucosal adjuvant comprised of a

vaccine antigen and IFN-α, wherein the vaccine antigen is a protein or peptide antigen, the IFN-α is natural IFN-α, and wherein said nasal mucosal administration of said mucosal adjuvant/vaccine antigen induces both vaccine antigen-specific antibody in blood and vaccine antigen-specific antibody secreted at the mucosal surface. The claims further recite specific amounts of IFN-α, and locations for inducting of vaccine-specific antibody and specific types of antibodies.

Staats teaches a method of eliciting an immune response by administration of a vaccine antigen and an adjuvant (see abstract, and claim 1). Staats teaches that the vaccine antigen can be either protein or peptide antigens, including protein/peptide antigens from a number of pathogenic organisms (see p. 21, line 11 – p. 23, line 2). Staats also teaches that various cytokines can be used as adjuvants (see p. 14, line 19 – p. 15, line 2, and claims 5-6). Furthermore, Staats teaches mucosal administration of the vaccine-adjuvant combination (claim 17), and also teaches that the vaccine-adjuvant induces both systemic (claim 22) and mucosal (claim 25) immune responses. Finally, by teaching that the vaccine and adjuvant are included together as a composition, Staats teach that the vaccine antigen and the adjuvant are administered at the same time and by the same route of administration. However, Staats is silent regarding the use of IFN-α as the adjuvant for any antigen-adjuvant combination or composition.

Takasu teaches that IFN-α is a potent adjuvant for increasing the immune response to various vaccine antigens. Specifically, Takasu discloses that co-administration of IFN-α with influenza virus peptide increased the cytotoxic T lymphocyte (CTL) response to the influenza virus peptide compared to vaccination with the influenza virus peptide alone (see p. 172-174, Figures 1-3).

In the response received on 8/29/2007, the Applicants argue that the instant invention is not obvious in view of Staats and Takasu because Staats teaches a method wherein IFN-γ is used, rather than IFN-α, and furthermore, Staats does not teach or suggest a systemic immune and a mucosal immune response induced by concomitant use of IFN-α and an antigen by nasal administration. The Applicants also argue that Takasu teaches away from the present invention because it teaches that the antigen peptide continuous administration via an osmotic pump and IFN-α administration by injection, thus providing no teaching or suggestion of nasal administration. Furthermore, the Applicants point to data presented within the examples of the instant specification showing higher antibody titers induced by a method of nasal administration of a protein antigen and IFN-α compared to nasal administration of a protein antigen alone. Therefore, the Applicants argue that the claims cannot be obvious due to unexpectedly improved properties compared to the prior art.

These arguments have been fully considered and are not persuasive. The combination of Staats and Takasu provide a person of ordinary skill in the art with the knowledge that vaccine antigens,

including peptide and protein antigens, can be administered with cytokine adjuvants in methods of mucosal administration (Staats), and that IFN-α is an effective adjuvant for protein antigens (Takasu). Therefore, one of ordinary skill in the art would have the motivation to use IFN-α as the cytokine adjuvant in the mucosal vaccine of Staats. Regarding Applicants arguments that the claimed mucosal adjuvants and/or combined products possess unpexpectedly improved properties, one of ordinary skill in the art would expect a vaccine composition comprising a peptide/protein vaccine antigen and an IFN-α adjuvant to induce higher antibody titers compared to vaccine antigen along due to the teachings of Takasu. Thus, the results provided by the instant invention would not be surprising to one of ordinary skill in the art.

Furthermore, regarding Applicants arguments that the combination of Staats and Takasu do not suggest or teach nasal administration, it is noted that Staats teaches mucosal administration of vaccine/adjuvant compositions. Because one of ordinary skill in the art would know of various, limited numbers of mucosal vaccination routes, including nasal, one of ordinary skill would thus be motivated, via ordinary skill and common sense, to determine the most suitable route of administration. When there is motivation to solve a problem and there are a finite number of identified, predictable solutions (in the instant case, limited numbers of mucosal administration routes), a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try may show that it was obvious under § 103 (*KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d 1385, 1397 (2007)).

Finally, it is noted that Takasu teaches use of IFN-α as an adjuvant at 10^6 U, which is within the claimed dosage range. Furthermore, neither Staats nor Takasu specifically teach vaccine antigen-specific antibody secreted at the gastrointestinal mucosal surface, wherein said antibody if IgA, or vaccine antigen-specific antibody in the blood wherein said antibody is IgG. However, it would be expected, in absence of evidence to the contrary, that a nasally administered composition comprising a vaccine antigen and an IFN-α adjuvant, as is obvious in view of Staats and Takasu, would induce vaccine-antigen specific antibodies at the gastrointestinal mucosal surface and in the blood, wherein said antibodies are IgA and IgG, respectively.

2. Claims 7, 9, 13, 15, and 19 *remain rejected*, and new claims 31-39 are also rejected under 35 USC § 103(a) as being obvious in view of the combination of Foster et al ("Foster", US 6,436,391) and

Tovey (US 6, 361,769), as set forth on pages 4-5 of the office action mailed on 5/29/2007 and pages 7-8 of the office action mailed on 12/14/2006.

The subject matter of the claims of the instant invention is discussed *supra*. Foster teaches the use of IFN-α as a vaccine adjuvant to increase B lymphocyte proliferation, and thus increase the effectiveness of vaccines (column 1, lines 52-56), and specifically recites co-administration of a vaccine with IFN-α, or alternatively, a composition comprised of IFN-α and a vaccine (column 1, lines 61-65). Foster is silent regarding mucosal administration of an IFN-α vaccine-adjuvant composition, and is also silent regarding specific amounts or doses of IFN-α.

Tovey teaches a method of stimulating host immunity by oromucosal administration of IFN-α (column 2, line 32 – column 3, line 28). Tovey discloses specific doses of IFN-α that can be oromucosally administered (column 3, line 15-20), and also teaches that IFN-α can be administered as an adjunct to other therapy (column 3, lines 21-22), and specifically mentions previous studies in which IFNs where orally administered to enhance the efficiency of vaccines (column 1, lines 61-66).

In the response received on 8/29/2007, the Applicants argue that Foster does not teach or suggest administration of natural IFN-a with a peptide or protein antigen nasally at the same time, and Tovey does not teach or suggest a mucosal adjuvant comprising natural IFN-α and a protein or peptide antigen, that when administered nasally would elicit a systemic immune response as well as a mucosal immune response. The Applicants further assert that because the currently claimed mucosal adjuvant comprising natural IFN-α and a vaccine antigen induces a systemic immune response as well as a mucosal immune response, the claims of the invention cannot be obvious in view of the art.

These arguments have been fully considered and are not persuasive. Both Foster and Tovey teach the use of IFN-α as a vaccine adjuvant, and Tovey specifically recites oromucosal administration of IFN-α to enhance the efficiency of vaccines. Thus, the combination of Foster and Tovey would provide one of ordinary skill in the art with the motivation to create a mucosal adjuvant comprising a peptide/vaccine antigen and IFN-α, because Tovey teaches that such compositions can be administered oromucosally, and Foster teaches increased effectiveness of vaccines administered with IFN-α. Although neither reference specifically recites "natural" IFN-α, there is no disclosed differences between "natural" IFNs and recombinant IFNs that would lead a person of ordinary skill in the art to specifically select "natural" IFN-α over recombinant IFN-α. Because both are IFN-α polypeptides, and a recombinant IFN can have the same amino acid sequence as a "natural" IFN, one would expect them to have identical functions. Furthermore, although neither Foster nor Tovey specifically recite nasal administration, it is noted that

Tovey teaches oromucosal administration of IFN-α to increase the efficiency of vaccines. Because one of ordinary skill in the art would know of various, limited numbers of oromucosal vaccination routes, including nasal, one of ordinary skill would thus be motivated, via ordinary skill and common sense, to determine the most suitable route of administration. When there is motivation to solve a problem and there are a finite number of identified, predictable solutions (in the instant case, limited numbers of oromucosal administration routes), a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try may show that it was obvious under § 103 (*KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d 1385, 1397 (2007)).

Finally, although, neither Foster nor Tovey specifically teach vaccine antigen-specific antibody secreted at the gastrointestinal mucosal surface, wherein said antibody is IgA, or vaccine antigen-specific antibody in the blood wherein said antibody is IgG. However, it would be expected, in absence of evidence to the contrary, that a nasally administered composition comprising a vaccine antigen and an IFN-α adjuvant, as is obvious in view of Foster and Tovey, would induce vaccine-antigen specific antibodies at the gastrointestinal mucosal surface and in the blood, wherein said antibodies are IgA and IgG, respectively.

Conclusion

No claim is allowable.

All claims are drawn to the same invention claimed in the parent application prior to the filing of this Continued Prosecution Application under 37 CFR 1.53(d) and could have been finally rejected on the grounds and art of record in the next Office action. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing under 37 CFR 1.53(d). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571) 272-3324. The examiner can normally be reached M-F from 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached at (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Bruce D. Hissong
Art Unit 1646

/Robert S. Landsman/
Primary Examiner, Art Unit 1647